REMARKS

Claims 19-48 are currently pending. Applicant note that the first page of the office action erroneously lists claims 19-49 as pending, when there are only 48 claims. Claims 42 and 43 have been amended, and claims 38, 40-41, and 46-47 have been canceled. The amendments to claims 42 and 43 are supported by the specification do not constitute new matter.

The Examiner has rejected claims 19-48 under 35 U.S.C. § 112, first paragraph, as lacking support in the written description. The Examiner has rejected claims 38, 40, 41, 43, 46, and 47 under 35 U.S.C. § 102(b) as being anticipated by Iacono *et al.* (Am. J. Respir. Care Med., 1997, 155:1690-1698) ("Iacono"). The Examiner has rejected 19-48 under 35 U.S.C. § 103(a) over Adjei *et al.* (U.S. Patent No. 5,635,161) ("Adjei") and Waldrep *et al.* (U.S. Patent No. 5,958,378) ("Waldrep") in view of Knight et al. (U.S. Patent No. 5,049,388) ("Knight"), Gordon *et al.* (U.S. Patent No. 6,572,893) ("Gordon"), and Iacono. For the reasons detailed below, the rejections should be withdrawn and the claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

The Claims Are Supported In The Written Description

The Examiner has rejected claims 19-48 under 35 U.S.C. § 112, first paragraph, as lacking support in the written description. The Examiner states that

> "[i]t is recognized the application disclose the genius [sic] (cyclosporine in general) and particular species of non-encapsulated cyclosporine (the examples). However, the application lacks a proper written description for the subgenus 'non-encapsulated cyclosporine.'"

Applicant submit that a person of ordinary skill in the art would understand that the cyclosporine formulations of the present invention are not encapsulated, and therefore "non-encapsulated cyclosporine" need not be explicitly recited in the specification. MPEP § 2163 ("If

a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met."). Applicant note that claim limitations may "be supported in the specification through express, implicit, or inherent disclosure." *Id.*

Applicant submits that a person of ordinary skill in the art would understand that the cyclosporine compositions of the present invention are not encapsulated. Applicant note that the dry powder described in the specification is a plain, dry powder which is not encapsulated. See page 19, line 13 to page 21, line 2. Alternatively, the cyclosporine is dissolved in various solvents, such as propylene glycol. See page 29, lines 1-16. Applicant notes that the solvents disclosed in the present invention, for example, propylene glycol, are not lipids, and therefore would not encapsulate the dissolved cyclosporine to form liposomes. Similarly, there is no indication that any of the dry powder compositions or dissolved formulations would result in an encapsulated cyclosporine. Furthermore, the Examiner has not supplied any evidence to show that the cyclosporine compositions of the present invention would be encapsulated. See MPEP § 2164.04. Thus, the present invention implicitly supports the limitation of "non-encapsulated cyclosporine." See MPEP § 2163, *supra*. Accordingly, a person of ordinary skill in the art would understand that the cyclosporine compositions of the present invention are not encapsulated, because they are either used as a dry, unmodified powder, or are dissolved in standard solvents.

Accordingly, Applicant submits that the Examiner's rejection for lack of written description has been obviated, and respectfully requests that the rejection be withdrawn.

The Anticipation Rejection Has Been Obviated

The Examiner has rejected claims 38, 40, 41, 43, 46, and 47 under 35 U.S.C. § 102(b) as being anticipated by Iacono *et al.* (Am. J. Respir. Care Med., 1997, 155:1690-1698) ("Iacono"). The Examiner states that Iacono "teaches a cyclosporin composition for aerosol delivery consisting of cyclosporin, a solvent and a propellant and the method of using the same for treating lung graft rejections."

Without making concessions, claims 38, 40-41, and 46-47 have been canceled. Claims 42 and 43 have been amended to reflect new dependencies. Accordingly, Applicant submits that the Examiner's rejection has been obviated and respectfully request withdrawal of the rejection.

The Claims Are Not Obvious

The Examiner has rejected 19-48 under 35 U.S.C. § 103(a) over Adjei *et al.* (U.S. Patent No. 5,635,161) ("Adjei") and Waldrep *et al.* (U.S. Patent No. 5,958,378) ("Waldrep") in view of Knight *et al.* (U.S. Patent No. 5,049,388) ("Knight"), Gordon *et al.* (U.S. Patent No. 6,572,893) ("Gordon"), and Iacono. The Examiner asserts that Waldrep and Adjei "teach that cyclosporins are old and well known... in various dosage forms, particularly, aerosol dosage form," and states that Waldrep and Adjei "do not teach expressly the various unencapsulated dosage form, or the dosage levels herein claimed, or the particular time herein claimed." The Examiner asserts that Knight and Gordon teach the dry powder form, and that Iacono teaches aerosol delivery. According to the Examiner, it would have been obvious to administer the cyclosporine within 10 days after transplantation "because cyclosporins are known to be useful for organ transplantation patients and are known for treating inflammatory diseases herein."

The Examiner states that the remarks made in the previous amendment, submitted January 15, 2004, are moot because Iacono and Gordon both teach non-encapsulated cyclosporine. Applicant submits that Iacono and Gordon do not reduce the force of the remarks made in the previous response, nor do they provide all of the missing limitations. To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See MPEP §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

As noted in the previous response, the references cited by the Examiner do not teach all of the limitations of the present claims; in particular, the references, alone or in combination, do not teach the limitation of administration "within 10 days following transplantation or prior to the development of symptoms associated with transplant rejection." See Amendment filed January 15, 2004, page 12, already of record (the "January 15, 2004 Amendment"). Iacono and Gordon do not alleviate this deficiency. Iacono discloses administration of aerosolized cyclosporine, on average, approximately *one year* after transplantation. Iacono at page 1691, left column. Indeed, at the earliest, patients were administered aerosolized cyclosporine 91 days after transplantation. Iacono at Table 1, page 1692. Gordon is directed to a method of spray drying drugs, and does not provide any guidance regarding when to administer aerosolized cyclosporine. Accordingly, none of the references provides the missing limitation of

administration "within 10 days following transplantation or prior to the development of symptoms associated with transplant rejection."

The Examiner asserts that it would be obvious to administer aerosolized cyclosporine directly following transplantation. However, Applicant submits that the Examiner is improperly making a determination of obviousness based on impermissible hindsight. See *In re Dow Chemical Co.*, 837 F.2d 469, 473 , 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988) (The suggestion or motivation to combine "must be found in the prior art, not in the applicant's disclosure.... There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure."). The references cited by the Examiner do not disclose administration of aerosolized cyclosporine directly after transplantation; the only reference cited by the Examiner which discloses a time frame for administration, Iacono, in fact suggest administration well after transplantation. Accordingly, Applicant's submit that the Examiner is improperly drawing the timing limitation from the Applicant's disclosure.

Applicant submits that there is no suggestion or motivation to administer the aerosolized cyclosporin within 10 days of transplantation or prior to the development of symptoms. The Examiner merely states that cyclosporine was known to be useful for transplantation patients and for treating inflammatory disease, and that the "skilled artisan would have possessed all conventional administration regimens, and seen the selection of one or another as the simple selection of obvious alternatives." However, the Examiner has not provided any evidence that administration "within 10 days following transplantation or prior to the development of symptoms associated with transplant rejection" was a "conventional administration regimen." The Examiner is suggesting that, at best, it was *possible* at the time of filing the application to do so; however, this is insufficient to provide a suggestion or motivation to administer cyclosporine

directly following transplantation. MPEP § 2143.01 ("The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.") (emphasis in original). None of the references cited by the Examiner provides any specific reason why immediate administration of aerosolized cyclosporine would be desirable, and therefore provide no suggestion or motivation to do so. Iacono and Gordon do not provide the missing suggestion or motivation, because, as noted above, neither reference teaches administration immediately following transplantation.

Because Iacono and Gordon do not provide the missing limitations nor do they supply the suggestion or motivation necessary, Applicant submits that the remarks set forth in the previous response apply to the present rejection. In particular, Applicant notes that Waldrep, Gilbert, and Knight do not teach administration directly following transplantation. See January 15, 2004 Amendment at page 12. Furthermore, disclosure of liposomal cyclosporine formulations in fact teach away from the present invention. *Id.*, at pages 13-17. Applicant hereby incorporates by reference the arguments previously set forth in the January 15, 2004 Amendment.

Based upon the foregoing remarks, and the remarks set forth in the January 15, 2004 Amendment, Applicant submits that the Examiner's rejection under 35 U.S.C. § 103(b) has been obviated, and respectfully requests that the rejection be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the inventions described and defined by claims 19-48 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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